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(54) Title: PROCESS FOR PARALLEL SYNTHESIS OF A NON-PEPTIDE LIBRARY

(57) Abstract

A process for the sequential preparation of a library of compounds having pharmaceutical usage. The process involves the sequential mixing of solution phase reagents, followed by scavenging of excess unreacted reagents with solid phase scavenging agents. The process is highly iterative and applicable for producing various ureas, thiureas, amides, carbonates and tertiary amines.

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# PROCESS FOR PARALLEL SYNTHESIS OF A NON-PEPTIDE LIBRARY

## Background of the Invention

Pharmaceutical research and development expenses account for the largest outlay of capital in the industry. Most recent studies indicate that the cost to discover and develop a drug candidate which is eventually brought to market is roughly four hundred million dollars. Equally daunting is the time required to finally launch the product - roughly eleven years is the average time lag, measured from the first discovery of the novel compound.

Conventional methods of synthesis are to "blame" for the inordinate costs and delays of drug discovery research. Prior methods emphasized the synthesis of individual compounds for activity testing, followed by development of analogs in the event of a successful result (or "hit") in an effort to develop a thorough structure - activity relationship (SAR) and determine the most likely candidate for lead compound status.

This synthesis of individual compounds is the most expensive and time consuming phase of discovery research. Based upon the principles of "rational design", research chemists would synthesize hundreds of analogs of high purity for screening in order to fully develop the SAR. Although this rational design method worked better than its predecessor, the hit or miss random approach, the limitations of manual synthesis, coupled with the desire for high purity compounds at this initial phase of discovery, considerably slowed the development process.

The need for more rapid and less expensive discovery research is critical in the ever-evolving industry of drug development. It has become all too clear that reliance on the old paradigms of individual compound synthesis, followed by SAR development, is a slow road to oblivion. To compete in the 1990's and in the future, drug development companies must meet the challenge of rapidly developing new and

innovative medicines, and in a manner which minimizes the research costs.

The currently accepted method of generating large numbers of compounds, referred to generically as "libraries", has been known in some form since the early 1960's. For nearly thirty years, the only efforts at library generation were in the peptide synthesis field. Even today, the majority of libraries generated by parallel synthesis methods are peptide or peptide-like compounds.

The parallel synthesis of peptide libraries carries advantages and disadvantages. Among the obvious advantages are the ability to theoretically generate huge numbers of compounds in a very short time period. Automated peptide synthesizers can provide for the creation of a theoretical number of peptides which increases exponentially as the number and variety of amino acid building blocks is increased. Examples of the numbers of peptides which are theoretically formed may be viewed in any of a number of prior art references, in both patents and publications.

Disadvantages of peptides include poor oral availability and rapid changing times, which significantly reduces the chance that a lead compound will be developed much further than the initial phase. Further, the generation of huge libraries includes the synthesis of (theoretically) thousands of compounds in each vessel. Although a number of methods and devices have been suggested to assist in identification of individual compounds, the problem remains - identification of the specific active compound (or in some cases, combination of compounds) is extremely difficult and in some cases even more expensive and time-consuming than traditional methods.

Parallel synthesis of "small" molecules (non-oligomers with a molecular weight of 200-1000) was rarely attempted prior to 1990. F. Camps, et.al., Annaks de Quimica 70,848, disclosed a synthesis of four related benzodiazepines via solid phase parallel synthesis. Recently, Professor Ellmann of the University of California at Berkeley has disclosed the

solid phase-supported parallel (also referred to as "combinatorial") synthesis of eleven benzodiazepine analogs along with some prostaglandins and beta-turn mimetics. These disclosures are exemplified in U.S. Patent 5,288,514 and in numerous publications, which will be found in the Information Disclosure Sheet to be submitted in support of this application. Another relevant disclosure of parallel synthesis of small molecules may be found in U.S. Patent 5,324,483. This patent discloses the parallel synthesis of between 4 and 40 compounds in each of sixteen different scaffolds.

Parallel, or combinatorial, synthesis has as its primary objective the generation of a library of diverse molecules which all share a common feature, referred to throughout this application as a scaffold. By substituting different moieties at each of the variable parts of the scaffold molecule, the amount of space explorable in a library grows. Theories and modern medicinal chemistry advocate the concept of occupied space as a key factor in determining the efficacy of a given compound against a given biological target. By creating a diverse library of molecules which explores a large percentage of the targeted space, the odds of developing a highly efficacious lead compound increase dramatically.

Parallel synthesis is generally conducted on a solid phase support normally on a polymeric resin. The scaffold, or other suitable intermediate is cleavably tethered to the resin by a chemical linker. Reactions are carried out to modify the scaffold while tethered to the solid support. Variations in reagents and/or reaction conditions produce the structural diversity which is the hallmark of each library.

As known in the art, parallel synthesis schemes are usually carried out in 96 well microtiter plates. The number of compounds desired to be produced will normally depend upon the range of space to be explored, usually from about 200 or 300 compounds up to more than 100,000. Theoretically, the total number of compounds which could be produced for a given

library is limited only by the number of reagents available and the number of variable positions on the scaffold.

The greatest advantage of parallel synthesis is its adaptability to automation procedures. Once the actual reactions have been validated and confirmed, an entire library of compounds can usually be produced in less than a week. Considering that a typical research chemist manually synthesizes about 10-15 compounds per month, the speed and cost advantages of parallel synthesis are borne out.

The main disadvantage of parallel synthesis is purity, or more specifically, lack of purity. Since the same reaction conditions are used for all 96 compounds (assuming one compound per well), yields and purity may fluctuate greatly across the plate. This can cause false positive or negative results and may skew the overall data generated by the library. This disadvantage is lessened by utilizing proven and highly reliable methods of synthesis for the functionalized scaffolds to be produced.

After initially synthesizing and cataloging the library, the compounds are screened for potential biological activity. Active compounds are identified for secondary and tertiary screening, until a promising lead compound is identified for optimization and further work. Inactive compounds are held for future use against other potential targets.

Scaffolds are chosen for inclusion into a library based upon several factors such as size, known medicinal properties, known biological activity and pharmacaphoric properties, as well as ease of synthesis and the achievement of consistent yields and purity throughout the library. The functional groups used to modify the scaffold and product the sought-for molecular diversity are selected in much the same fashion.

## Summary of the Invention

This invention relates to processes for parallel production of a library of diverse non-peptide compounds. The process, as disclosed, differs from conventional parallel

synthesis in that the preferred reactions are carried out in solution phase. Solid phase supported scavengers are employed to remove excess reagents often used to drive a particular reaction to completion.

This general reaction scheme can be employed with any suitable scaffold. For purposes of this disclosure, the solution-phase process is disclosed as useful in making compounds of the following general formula:

$$R^2 - \underset{\displaystyle A}{\underset{|}{N}} - X - R^1$$

wherein A is an indole analog;

X is a bond, or X is carbonyl, or thiocarbonyl;

$R^1$ is hydrogen, $C_1$-$C_6$ alkyl, aryl, cycloalkyl, heterocycle $NR^3R^4$ or $OR^5$;

$R^2$ is hydrogen, $C_1$-$C_6$ alkyl, aryl, cycloalkyl, heterocycle or a substituted analog of any of the above; with the provision that $R^1$ and $R^2$ are not both hydrogen when X is a bond;

R3 and R4 are each individually hydrogen, C1-C6 alkyl, aryl cycloalkyl, heterocycle or a substituted analog of any of the above; and

$R^5$ is hydrogen, $C_1$-$C_6$ alkyl, aryl, cycloalkyl or a substituted analog of any of the above;

The process is described in detail in the following specification and generally includes two steps: mixing reactable compounds to produce the formula (I) compounds in a parallel fashion; and scavenging off any excess unreacted reagents with solid phase supported scavenger reagents, filtering off the solid phase bound waste.

## Detailed Description of the Invention

The detailed description of the invention which follows is not intended to be exhaustive or to limit the invention to the precise details disclosed. It has been chosen and described to best explain the details of the invention to others skilled in the art.

## Definitions of Terms Used

"Scaffold" means that part of the molecule which is common to all compounds formed by a combinatorial synthesis process.

"Combinatorial Synthesis Process" means an ordered process for the parallel synthesis of a large number of diverse molecules. This process is generally represented by one or more side chain matrices and a scaffold and is carried out in a number of separate reaction wells on a plate. Numerous plates, each having a number of separate reaction wells make up the library of compounds produced by the process. The side chain matrices identify the variable functional groups and the combinations of each with respect to the scaffold. In the case of two variable side chains, the matrix will resemble a table having "x" columns and "y" rows to illustrate the configurations generated.

"Functional Groups" are moieties which are bonded to the scaffold through the combinatorial synthesis process. The different functional groups account for the diversity of molecules throughout the library, and are selected to impart biological activity to the scaffold.

"Protecting Groups" are moieties attached to the reactive part(s) of the molecule which prevent a given reaction at that site. The presence of protecting groups allows one to control the synthesis more precisely at diverse areas of the scaffold, and the attached functional groups.

"Library" means a collection of compounds all having the same or similar scaffold, and diverse combinations of functional groups. A library is generally prepared by a combinatorial synthesis process.

Definitions of reactant and side chain terms used herein are as follows:

"$C_x$-$C_y$ alkyl" means a straight or branched chain hydrocarbon of between x and y carbon atoms.

"Aryl" means one or more aromatic rings, each of 5, 6, or 7 carbon atoms. Multiple aryl rings may be fused, as in naphthyl, or unfused, as in biphenyl.

"Substituted Aryl" means the same as aryl, but having one or more side chain moieties bonded to one or more of the ring carbon atoms. Side chain moieties disclosed as representative examples only in this application include alkyl, alkoxy, halo, cyano, $CF_3$, aryl, aryloxy, hydroxy, and COOR where R is hydrogen or alkyl.

"$C_x$-$C_y$ alkoxy" means a straight or branched chain hydrocarbon which is bonded to the scaffold by an oxygen atom to form an ether.

"Heterocycle" means one or more rings of 5, 6, or 7 atoms with at least one ring atom which is not carbon. Preferred heteroatoms include sulfur, oxygen, nitrogen, and phosphorous. Multiple rings may be fused, as in quinoline or benzofuran. "Substituted heterocycle" means heterocycle with one or more side chains, as in substituted aryl.

"$C_x$-$C_y$ Cycloalkyl" means a ring of between x and y carbon atoms having at least one fully saturated bond. "Substituted cycloalkyl" means a cycloalkyl with one or more side chains as defined above.

"Acyl" means an alkyl or aryl group bonded to the scaffold or side chain by a carbonyl moiety.

"Halo" means chloro, fluoro, iodo or bromo.

"Acyloxy" means an acyl group bonded to the scaffold or side chain by an oxygen atom.

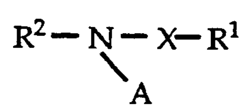
"Alkoxycarbonyl" means an alkoxy group bonded to the scaffold or side chain by a carbonyl moiety.

Other moieties retain their well-known definitions to those skilled in the art. Representative examples of each moiety have been left out of this section in the interests of clarity. Representative specific examples are identified in the schemes and matrices which follow to provide those skilled in the art with insights into the diverse structures obtained and obtainable through a combinatorial synthesis process.

This invention provides for methods of producing compounds in parallel fashion, with the compounds making up a diverse chemical library. All of the compounds in the library have a common backbone, referred to as the scaffold, and diverse functional groups attached to the scaffold. The functional groups are selected to allow the creation of a chemically diverse library which maximizes the exploration of molecular spatial properties. Such maximization increases the odds of creating compounds which will be biologically active against selected targets.

The library of compounds of this invention each have as their common scaffold the following molecule (the A, $R^1$,$R^2$ and X variables retain their earlier stated meanings:

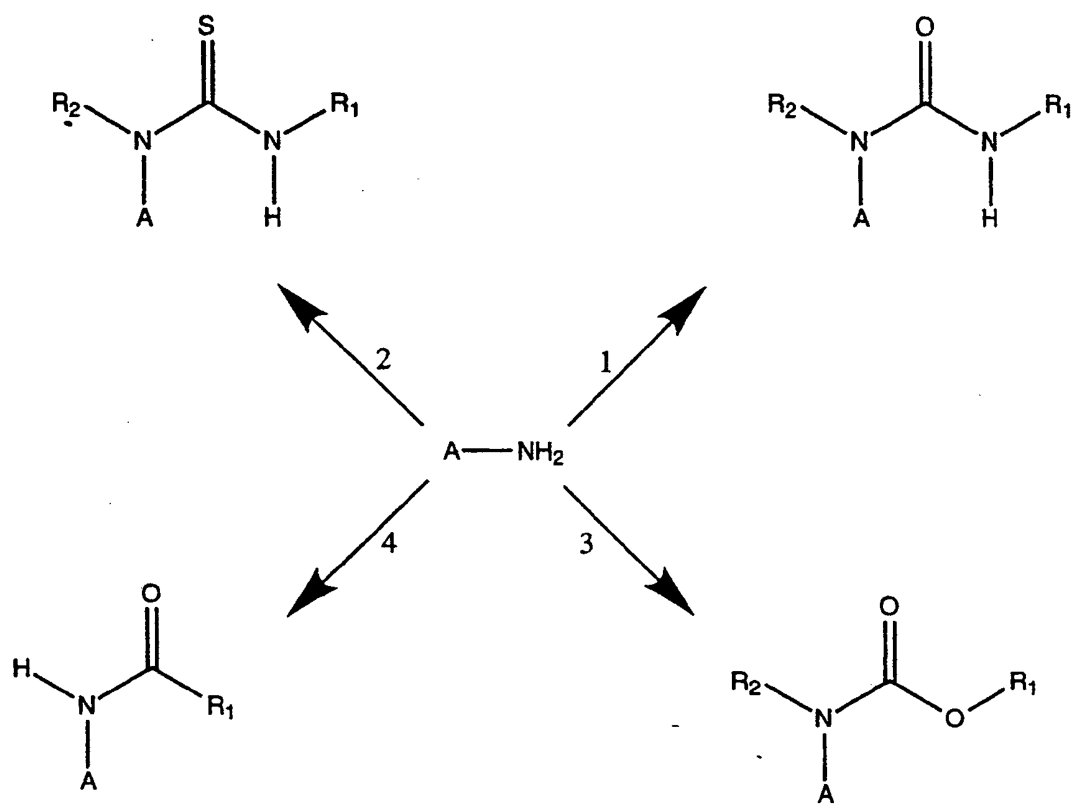
(I)




The library of compounds disclosed above is created with the objective of exploring the maximum amount of space. By creating a library of diverse molecules, each of which has a definite volume distinct from the other molecules, the chances of achieving successful results (i.e. positive screening results, lead generation, meaningful data

generation) is amplified. In the above library of compounds, the variable moieties are the elements of the molecule which create the desired diversity.

The general schemes and specific examples disclosed below are indicative of the serial (or combinatorial) processes which are used to produce the compounds which make up the library.



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This invention is a process for serially making a library of pharmaceutically useful compounds of the general formula:

$$\begin{array}{c} R^2 - \underset{\displaystyle |\atop\displaystyle A}{N} - X - R^1 \end{array}$$

wherein A is an indole analog;

X is a bond, or X is carbonyl, or thiocarbonyl;

$R^1$ is hydrogen, $C_1$-$C_6$ alkyl, aryl, cycloalkyl, heterocycle $NR^3R^4$ or $OR^5$;

$R^2$ is hydrogen, $C_1$-$C_6$ alkyl, aryl, cycloalkyl, heterocycle or a substituted analog of any of the above; with the provision that $R^1$ and $R^2$ are not both hydrogen when X is a bond;

R3 and R4 are each individually hydrogen, C1-C6 alkyl, aryl cycloalkyl, heterocycle or a substituted analog of any of the above; and

$R^5$ is hydrogen, $C_1$-$C_6$ alkyl, aryl, cycloalkyl or a substituted analog of any of the above;

said process comprising the steps of:

a) providing a first reagent in solution phase of the general formula:

$$A\text{-}NHR^2;$$

b) providing a series of second solution phase reagents each one of the general formulas:

(i) Y-X-$R^1$ wherein Y is a halogen and X i not a bond; or

(ii) Z-N-$R^1$ wherein Z is =C=O, =C=S or $R^1$-C(O)Y; and

c) sequentially mixing a predetermined quantity of said first reagent with predetermined quantities of diverse molecules of said second

reagents to create a library of Formula (I) compounds.

The process of the invention is preferably one wherein step (c) includes adding an excess of each said second reagents, then adding a scavenging agent, wherein excess unreacted second reagents are consumed and tethered to a solid phase. A preferred form of the process of the invention is one having an additional step (d) of filtering off the solid phase.

The process of the invention is preferably conducted in a multiple well reaction vessel, and a single one of the second reagents is introduced into each of the multiple wells.

The process of the invention is preferably one wherein each second reagent is of the general formula:

Y-X-$R^1$ wherein X is carbonyl, and $R^1$ is $NR^3R^4$.

Alternatively, the process of the invention is one wherein each second reagent is of the general formula:

Y-X-$R^1$ where X is carbonyl and $R^1$ is $OR^5$.

Alternatively, the process of the invention is one wherein each second reagent is of the formula:

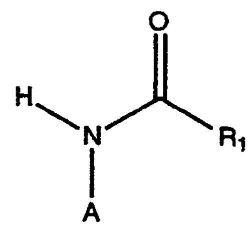
Y-X-$R^1$ where $R^1$ is hydrogen, $C_1$-$C_6$ alkyl, aryl, cycloalkyl, heterocycle, or substituted analog thereof.

Alternatively, the process of the invention is one wherein each second reagent is of the general formula:

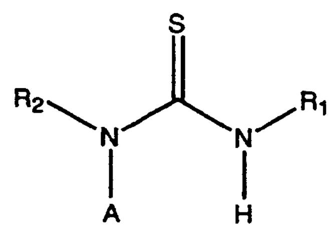
Z-N-$R^1$ where Z is carbonyl.

Preferably the process of the invention is one whererin wherein $R^2$ is hydrogen.

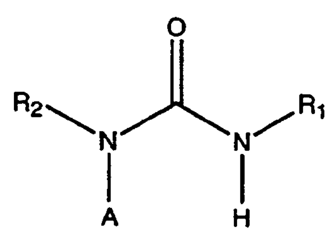
The process of the invention may be used to prepare compounds wherein the formula (I) compounds have the structure:



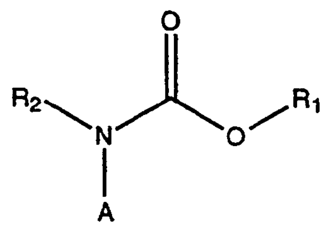
Alternatively, the process of the invention may be used to prepare compounds wherein the formula (I) the formula (I) compounds have the structure:



Alternatively, the process of the invention may be used to prepare compounds wherein the formula (I) compounds have the following structure:



Alternatively, the process of the invention may be used to prepare compounds wherein the formula (I) compounds have the following structure:



More generally, the process of the invention may be used to prepare diverse chemical libraries. A suitable scavenger process for preparing a library of structurally diverse compounds comprises the steps of:

a) providing a first reagent in solution phase;

b) providing a second reagent in solution phase, with the first and second reagents capable of reacting to form a product;

c) mixing said first reagent with an adequate amount of the second reagent to facilitate a complete reaction and form a mixture;

d) adding a solid phase-supported scavenger reagent to the mixture to remove unreacted quantities of said second reagent wherein the scavenger reagent reacts with the second reagent to form a solid support tethered compound; and

e) separating the product from the solid support tethered compound.

The general process of the invention is desirably a process step d) includes adding a polymeric resin bound scavenger reagent to the mixture, and step e) includes separating the solid support tethered compound from the product by filtration.

Preferably the general process of the invention is one wherein steps a) and b) include providing a plurality of structurally diverse first and second reagents wherein a plurality of structurally diverse products are formed.

Compounds of the invention where X-$R^1$ creates a urea or thiourea derivative are prepared by treating a solution of the 5-amino-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole or 5-amino-3-(piperidin-4-yl)-1H-indole in a suitable solvent, such as chloroform or dichloromethane, with an appropriate isocyanate, isothiocyanate, carbamoyl chloride or carbamoyl bromide. When a carbamoyl chloride or carbamoyl bromide is used, the reactions are performed in the presence of a suitable base. Suitable bases include amines typically used as acid scavengers, such as pyridine or triethylamine, or commercially available polymer bound bases such as polyvinylpyridine. If necessary, an excess of the isocyanate, isothiocyanate, carbamoyl chloride or carbamoyl bromide is employed to ensure complete reaction of the starting amine. The reactions are performed at about ambient to about 45°C, for from about three hours to about three days. Typically, the product may be isolated by washing the reaction with water and concentrating the remaining organics under reduced pressure. When an excess of isocyanate, isothiocyanate, carbamoyl chloride or carbamoyl bromide has been used, however, a polymer bound primary or secondary amine, such as an aminomethylated polystyrene, may be conveniently added to react with the excess reagent. Isolation of products from reactions where a polymer bound reagent has been used is greatly simplified, requiring only filtration of the reaction mixture and then concentration of the filtrate under reduced pressure. The product from these reactions may be purified chromatographically or recrystallized from a suitable solvent if desired.

Compounds of the invention where the functional group is a carbonate are prepared by reactindropyridin-4-yl)-1H-indole or 5-amino-3-(piperidin-4-yl)-1H-indole with an appropriately substituted chloroformate in the presence of a suitable amine

under the conditions described in the previous paragraph. Likewise, compounds of the invention where the functional group is an amide are prepared by reacting the 5-amino-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole or 5-amino-3-(piperidin-4-yl)-1H-indole with an appropriate carboxylic acid chloride, bromide or anhydride, optionally in the presence of an acylation catalyst such as dimethylaminopyridine, in the presence of a suitable base, such as those described *supra*.

EXAMPLE 1

5-(methoxycarbonyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

To a mixture of 10 mg (0.0437 mMol) 5-amino-3-(1-methyl-piperidin-4-yl)-1H-indole and 15.0 mg (.131 mMol) polyvinyl-pyridine in 3.0 mL dichloromethane were added 4.3 mg (0.0458 mMol) methyl chloroformate. The reaction mixture was mixed for 2 days at ambient temperature. To this mixture were then added 170 mg (0.137 mMol) aminomethylated polystyrene and the reaction mixed for an additional 18 hours. The reaction mixture was then filtered and the volatiles evaporated to give 10.2 mg (81%) of the title compound.

MS(m/e): 287($M^+$)

The compounds of Examples 2-8 were prepared by the procedure described in detail in Example 1.

EXAMPLE 2

5-(ethoxycarbonyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 10 mg (0.0437 mMol) 5-amino-3-(1-methyl-piperidin-4-yl)-1H-indole and 4.97 mg (0.0458 mMol) ethyl chloroformate, 11.1 mg (84%) of the title compound were recovered.

MS(m/e): 301($M^+$)

EXAMPLE 3

5-(propoxycarbonyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 10 mg (0.0437 mMol) 5-amino-3-(1-methyl-piperidin-4-yl)-1H-indole and 5.62 mg (0.0458 mMol) propyl chloroformate, 11.2 mg (81%) of the title compound were recovered.

MS(m/e): 316($M^+$)

EXAMPLE 4

5-(allyloxycarbonyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 10 mg (0.0437 mMol) 5-amino-3-(1-methyl-piperidin-4-yl)-1H-indole and 5.5 mg (0.0458 mMol) allyl chloroformate, 9.7 mg (71%) of the title compound were recovered.

MS(m/e): 314($M^+$)

EXAMPLE 5

5-((2-methoxyethyl)carbonyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 13 mg (0.0567 mMol) 5-amino-3-(1-methyl-piperidin-4-yl)-1H-indole and 8.65 mg (0.062 mMol) 2-methoxyethyl chloroformate, 10.25 mg (54%) of the title compound were recovered.

MS(m/e): 332($M^+$)

EXAMPLE 6

5-(cyclopentyloxycarbonyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 13 mg (0.0567 mMol) 5-amino-3-(1-methyl-piperidin-4-yl)-1H-indole and 9.27 mg (0.062 mMol) cyclopentyl chloroformate, 18.1 mg (93%) of the title compound were recovered.

MS(m/e): 342($M^+$)

EXAMPLE 7

5-(phenoxycarbonyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 10 mg (0.0437 mMol) 5-amino-3-(1-methyl-piperidin-4-yl)-1H-indole and 7.2 mg (0.0458 mMol) phenyl

chloroformate, 13.9 mg (91%) of the title compound were recovered.

MS(m/e): 350($M^+$)

EXAMPLE 8

5-(4-methoxyphenyl)oxycarbonyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 13 mg (0.0567 mMol) 5-amino-3-(1-methyl-piperidin-4-yl)-1H-indole and 11.1 mg (0.062 mMol) 4-methoxyphenyl chloroformate, 13.4 mg (63%) of the title compound were recovered.

MS(m/e): 380($M^+$)

EXAMPLE 9

5-(4-chlorophenyl)oxycarbonyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 13 mg (0.0567 mMol) 5-amino-3-(1-methyl-piperidin-4-yl)-1H-indole and 11.1 mg (0.062 mMol) 4-chlorophenyl chloroformate, 18.1 mg (93%) of the title compound were recovered.

MS(m/e):

EXAMPLE 10

N-ethyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

To a solution of 15.0 mg (.0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole in 3.0 mL dichloromethane were added 9.3 mg (.131 mMol) ethyl isocyanate. The reaction was mixed for 48 hours and to it was then added 0.23 gm (.131 mMol) aminomethylated polystyrene and the reaction mixed for an additional 18 hours. The reaction mixture was then filtered and the volatiles evaporated to give 16.1 mg (82%) of the title compound.

MS(m/e):

The compounds of Examples 11-32 were prepared by the procedure described in detail in Example 10.

EXAMPLE 11

N-propyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15.0 mg (.0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 11.1 mg (0.131 mMol) propyl isocyanate, 5.8 mg of the title compound were recovered.
MS(m/e): 315($M^+$)

EXAMPLE 12

N-allyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15.0 mg (.0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 11.1 mg (0.131 mMol) allyl isocyanate, 19.6 mg (96%) of the title compound were recovered.
MS(m/e): 313($M^+$)

EXAMPLE 13

N-isopropyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15.0 mg (.0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 11.13 mg (0.131 mMol) isopropyl isocyanate, 21.9 mg of the title compound were recovered.
MS(m/e): 315($M^+$)

EXAMPLE 14

N-n-butyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15.0 mg (.0655 mMol) 5-amino-3-(1-methyl-piperidin-4-yl)-1H-indole and 11.1 mg (0.131 mMol) n-butyl isocyanate, 20.6 mg (96%) of the title compound were recovered.

MS(m/e): 329($M^+$)

EXAMPLE 15

N-cyclohexyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15.0 mg (.0655 mMol) 5-amino-3-(1-methyl-piperidin-4-yl)-1H-indole and 16.37 mg (0.131 mMol) cyclohexyl isocyanate, 20.1 mg (87%) of the title compound were recovered.

MS(m/e): 355($M^+$)

EXAMPLE 16

N-(ethyl 3-methylbutyrate-2-yl)-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15.0 mg (.0655 mMol) 5-amino-3-(1-methyl-piperidin-4-yl)-1H-indole and 14.56 mg (0.0852 mMol) ethyl 2-isocyanato-3-methylbutyrate, 25.0 mg (95%) of the title compound were recovered.

MS(m/e): 401($M^+$)

## EXAMPLE 17

N-(4-fluoro)phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15.0 mg (.0655 mMol) 5-amino-3-(1-methyl-piperidin-4-yl)-1H-indole and 9.9 mg (0.072 mMol) 4-fluorophenyl isocyanate, 20.7 mg (86%) of the title compound were recovered.

MS(m/e): 367($M^+$)

## EXAMPLE 18

N-(4-chloro)phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15.0 mg (.0655 mMol) 5-amino-3-(1-methyl-piperidin-4-yl)-1H-indole and 11.0 mg (0.072 mMol) 4-chlorophenyl isocyanate, 21.4 mg (86%) of the title compound were recovered.

MS(m/e): 383($M^+$)

## EXAMPLE 19

N-(4-methyl)phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15.0 mg (.0655 mMol) 5-amino-3-(1-methyl-piperidin-4-yl)-1H-indole and 9.6 mg (0.072 mMol) 4-methylphenyl isocyanate, 23.7 mg (99%) of the title compound were recovered.

MS(m/e): 363($M^+$)

EXAMPLE 20

N-(3-trifluoromethyl)phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15.0 mg (.0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 16.0 mg (0.0852 mMol) 3-trifluoromethylphenyl isocyanate, 26.0 mg (95%) of the title compound were recovered.

MS(m/e): 417($M^+$)

EXAMPLE 21

N-(4-methoxy)phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15.0 mg (.0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 10.7 mg (0.072 mMol) 4-methoxyphenyl isocyanate, 22.4 mg (91%) of the title compound were recovered.

MS(m/e): 379($M^+$)

EXAMPLE 22

N-(2-methoxy)phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15.0 mg (.0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 10.7 mg (0.072 mMol) 2-methoxyphenyl isocyanate, 21.7 mg (88%) of the title compound were recovered.

MS(m/e): 379($M^+$)

EXAMPLE 23

N-(4-methylthio)phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15.0 mg (.0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 14.05 mg (0.0852 mMol) 4-methylthiophenyl isocyanate, 24.1 mg (93%) of the title compound were recovered.

MS(m/e): 395($M^+$)

EXAMPLE 24

N-(3-acetyl)phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15.0 mg (.0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 13.7 mg (0.0852 mMol) 3-acetylphenyl isocyanate, 25.0 mg (98%) of the title compound were recovered.

MS(m/e): 391($M^+$)

EXAMPLE 25

N-(4-carbobutoxy)phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15.0 mg (.0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 15.8 mg (0.072 mMol) 4-carbobutoxyphenyl isocyanate, 27.1 mg (92%) of the title compound were recovered.

MS(m/e): 449($M^+$)

EXAMPLE 26

N-(2-phenyl)phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15.0 mg (.0655 mMol) 5-amino-3-(1-methyl-piperidin-4-yl)-1H-indole and 16.6 mg (0.0852 mMol) 2-phenylphenyl isocyanate, 26.7 mg (96%) of the title compound were recovered.

MS(m/e): 425($M^+$)

EXAMPLE 27

N-(4-phenyl)phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15.0 mg (.0655 mMol) 5-amino-3-(1-methyl-piperidin-4-yl)-1H-indole and 16.6 mg (0.0852 mMol) 4-phenylphenyl isocyanate, 26.2 mg (95%) of the title compound were recovered.

MS(m/e): 425($M^+$)

EXAMPLE 28

N-(2,3-dichloro)phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15.0 mg (.0655 mMol) 5-amino-3-(1-methyl-piperidin-4-yl)-1H-indole and 16.0 mg (0.0852 mMol) 2,3-dichlorophenyl isocyanate, 26.7 mg (98%) of the title compound were recovered.

MS(m/e): 417($M^+$)

EXAMPLE 29

N-benzyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15.0 mg (.0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 11.32 mg (0.0852 mMol) benzyl isocyanate, 9.4 mg of the title compound were recovered.
MS(m/e): 363($M^+$)

EXAMPLE 30

N-phenethyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15.0 mg (.0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 12.51 mg (0.0852 mMol) 2-phenethyl isocyanate, 15.8 mg (65%) of the title compound were recovered.
MS(m/e): 377($M^+$)

EXAMPLE 31

N-(α-methylbenzyl)-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15.0 mg (.0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 12.51 mg (0.0852 mMol) α methylbenzyl isocyanate, 24.0 mg (97%) of the title compound were recovered.
MS(m/e): 377($M^+$)

EXAMPLE 32

N-(β-(ethoxycarbonyl)phenethyl)-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15.0 mg (.0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 16.6 mg (0.0852 mMol) ethyl 2-isocyanato-3-phenylpropionate , 28.0 mg (95%) of the title compound were recovered.
MS(m/e): 449($M^+$)

The compounds of Examples 33-36 were prepared at 45°C by the procedure described in detail in Example 1.

EXAMPLE 33

N,N-dimethyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 13.0 mg (.056 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 6.4 mg (0.059 mMol) dimethyl carbamoyl chloride, 13.2 mg (79%) of the title compound were recovered.

MS(m/e): 301($M^+$)

EXAMPLE 34

N,N-diethyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 13.0 mg (.056 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 8.0 mg (0.062 mMol) diethyl carbamoyl chloride, 16.05 mg (86%) of the title compound were recovered.

MS(m/e): 329($M^+$)

EXAMPLE 35

N-methyl-N-phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 13.0 mg (.056 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 10.1 mg (0.059 mMol) N-methyl-N-phenyl carbamoyl chloride, 17.4 (86%) of the title compound were recovered.

MS(m/e): 363($M^+$)

EXAMPLE 36

5-(morpholin-1-yl)carbonylamino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 13.0 mg (.056 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 8.9 mg (0.059 mMol) morpholine carbonyl chloride, 16.2 (85%) of the title compound were recovered.

MS(m/e): 343($M^+$)

The compounds of Examples 37-43 were prepared at 60°C by the procedure described in detail in Example 10.

EXAMPLE 37

N-methyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)thiourea

Beginning with 15.0 mg (.0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 9.56 mg (0.098 mMol) methyl isothiocyanate, 17.0 mg (86%) of the title compound were recovered.

MS(m/e): 303($M^+$)

EXAMPLE 38

N-phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)thiourea

Beginning with 15.0 mg (.0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 13.26 mg (0.098 mMol) phenyl isothiocyanate, 16.8 mg (71%) of the title compound were recovered.

MS(m/e): 365($M^+$)

EXAMPLE 39

N-(4-methoxy)phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)thiourea

Beginning with 15.0 mg (.0655 mMol) 5-amino-3-(1-methyl-piperidin-4-yl)-1H-indole and 16.21 mg (0.098 mMol) 4-methoxyphenyl isothiocyanate, 18.4 mg (71%) of the title compound were recovered.
MS(m/e): 395($M^+$)

EXAMPLE 40

N-(3-trifluoromethyl)phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)thiourea

Beginning with 15.0 mg (.0655 mMol) 5-amino-3-(1-methyl-piperidin-4-yl)-1H-indole and 19.94 mg (0.098 mMol) 3-trifluoromethylphenyl isothiocyanate, 15.6 mg (55%) of the title compound were recovered.
MS(m/e): 433($M^+$)

EXAMPLE 41

N-(2-phenyl)phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)thiourea

Beginning with 15.0 mg (.0655 mMol) 5-amino-3-(1-methyl-piperidin-4-yl)-1H-indole and 20.73 mg (0.098 mMol) 2-biphenyl isothiocyanate, 21.2 mg (74%) of the title compound were recovered.
MS(m/e): 441($M^+$)

EXAMPLE 42

N-(2,3-dichloro)phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)thiourea

Beginning with 15.0 mg (.0655 mMol) 5-amino-3-(1-methyl-piperidin-4-yl)-1H-indole and 20.04 mg (0.098 mMol) 2,3-dichlorophenyl isothiocyanate, 17.7 mg (62%) of the title compound were recovered.

MS(m/e): 433(M$^+$)

EXAMPLE 43

N-benzyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)thiourea

Beginning with 15.0 mg (.0655 mMol) 5-amino-3-(1-methyl-piperidin-4-yl)-1H-indole and 14.63 mg (0.098 mMol) benzyl isothiocyanate, 17.0 mg (86%) of the title compound were recovered.
MS(m/e): 379(M$^+$)

The compounds of Examples 44-53 were prepared by the procedure described in detail in Example 1.

EXAMPLE 44

5-(methoxyacetyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 13 mg (0.056 mMol) 5-amino-3-(1-methyl-piperidin-4-yl)-1H-indole and 6.5 mg (0.059 mMol) methoxy-acetyl chloride, 14.2 mg (84%) of the title compound were recovered.
MS(m/e): 302(M$^+$)

EXAMPLE 45

5-((2-thienyl)acetyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 13 mg (0.056 mMol) 5-amino-3-(1-methyl-piperidin-4-yl)-1H-indole and 9.6 mg (0.059 mMol) (2-thiophene)acetyl chloride, 14.1 mg (72%) of the title compound were recovered.
MS(m/e): 354(M$^+$)

EXAMPLE 46

5-(3-(methoxycarbonyl)propanoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 13 mg (0.056 mMol) 5-amino-3-(1-methyl-piperidin-4-yl)-1H-indole and 9.0 mg (0.059 mMol) (3-methoxy-

carbonyl)propanoyl chloride, 14.1 mg (75%) of the title compound were recovered.
MS(m/e): 344($M^+$)

EXAMPLE 47

5-(2-fluorobenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 10 mg (0.0437 mMol) 5-amino-3-(1-methyl-piperidin-4-yl)-1H-indole and 5.4 µ (0.0458 mMol) 2-fluorobenzoyl chloride, 12.2 mg (80%) of the title compound were recovered.
MS(m/e): 351($M^+$)

EXAMPLE 48

5-(2-methylbenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 10 mg (0.0437 mMol) 5-amino-3-(1-methyl-piperidin-4-yl)-1H-indole and 6.0 µ (0.0458 mMol) 2-methylbenzoyl chloride, 14.3 mg (95%) of the title compound were recovered.
MS(m/e): 348(M+1)

EXAMPLE 49

5-(3-methylbenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 13 mg (0.056 mMol) 5-amino-3-(1-methyl-piperidin-4-yl)-1H-indole and 9.2 mg (0.059 mMol) 3-methylbenzoyl chloride, 17.1 mg (88%) of the title compound were recovered.
MS(m/e): 348($M^+$)

EXAMPLE 50

5-(2-trifluoromethylbenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 13 mg (0.056 mMol) 5-amino-3-(1-methyl-piperidin-4-yl)-1H-indole and 13.0 mg (0.062 mMol) 2-trifluoromethylbenzoyl chloride, 20.3 mg (89%) of the title compound were recovered.
MS(m/e): 401($M^+$)

EXAMPLE 51

5-(3,4-dichlorobenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 10 mg (0.0437 mMol) 5-amino-3-(1-methyl-piperidin-4-yl)-1H-indole and 9.6 mg (0.0458 mMol) 3,4-dichlorobenzoyl chloride, 14.4 mg (82%) of the title compound were recovered.

MS(m/e): 401($M^+$)

EXAMPLE 52

5-(2,4-dichlorobenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 10 mg (0.0437 mMol) 5-amino-3-(1-methyl-piperidin-4-yl)-1H-indole and 6.4 µL (0.0458 mMol) 2,4-dichlorobenzoyl chloride, 12.2 mg (80%) of the title compound were recovered.

MS(m/e): 401($M^+$)

EXAMPLE 53

5-(isoxazol-5-oyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 13 mg (0.056 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 8.21 mg (0.062 mMol) isoxazole-5-carbonyl chloride, 10.4 mg (57%) of the title compound were recovered.

MS(m/e): 325($M^+$)

To demonstrate the use of the compounds of this invention in the treatment of migraine, their ability to bind to the 5-$HT_{1F}$ receptor subtype was determined. The ability of the compounds of this invention to bind to the 5-$HT_{1F}$ receptor subtype was measured essentially as described in N. Adham, *et al.*, *Proceedings of the National Academy of Sciences (USA)*, **90**, 408-412 (1993).

<u>Membrane Preparation:</u> Membranes were prepared from transfected Ltk- cells which were grown to 100% confluency. The cells were washed twice with phosphate-buffered saline, scraped from the culture dishes into 5 mL of ice-cold phosphate-buffered saline, and centrifuged at 200 x g for 5 minutes at 4°C. The pellet was resuspended in 2.5 mL of ice-cold Tris buffer (20 mM Tris HCl, pH=7.4 at 23°C, 5 mM EDTA) and homogenized with a Wheaton tissue grinder. The lysate was subsequently centrifuged at 200 x g for 5 minutes at 4°C to pellet large fragments which were discarded. The supernatant was collected and centrifuged at 40,000 x g for 20 minutes at 4°C. The pellet resulting from this centrifugation was washed once in ice-cold Tris wash buffer and resuspended in a final buffer containing 50 mM Tris HCl and 0.5 mM EDTA, pH=7.4 at 23°C. Membrane preparations were kept on ice and utilized within two hours for the radioligand binding assays. Protein concentrations were determined by the method of Bradford (*Anal. Biochem.*, **<u>72</u>**, 248-254 (1976)).

<u>Radioligand Binding:</u> [$^3$H-5-HT] binding was performed using slight modifications of the 5-$HT_{1D}$ assay conditions reported by Herrick-Davis and Titeler (*J. Neurochem.*, **<u>50</u>**, 1624-1631 (1988)) with the omission of masking ligands. Radioligand binding studies were achieved at 37°C in a total

volume of 250 µL of buffer (50 mM Tris, 10 mM $MgCl_2$, 0.2 mM EDTA, 10 µM pargyline, 0.1% ascorbate, pH=7.4 at 37°C) in 96 well microtiter plates. Saturation studies were conducted using [$^3$H]5-HT at 12 different concentrations ranging from 0.5 nM to 100 nM. Displacement studies were performed using 4.5-5.5 nM [$^3$H]5-HT. The binding profile of drugs in competition experiments was accomplished using 10-12 concentrations of compound. Incubation times were 30 minutes for both saturation and displacement studies based upon initial investigations which determined equilibrium binding conditions. Nonspecific binding was defined in the presence of 10 µM 5-HT. Binding was initiated by the addition of 50 µL membrane homogenates (10-20 µg). The reaction was terminated by rapid filtration through presoaked (0.5% poylethyleneimine) filters using 48R Cell Brandel Harvester (Gaithersburg, MD). Subsequently, filters were washed for 5 seconds with ice cold buffer (50 mM Tris HCl, pH=7.4 at 4°C), dried and placed into vials containing 2.5 mL Readi-Safe (Beckman, Fullerton, CA) and radioactivity was measured using a Beckman LS 5000TA liquid scintillation counter. The efficiency of counting of [$^3$H]5-HT averaged between 45-50%. Binding data was analyzed by computer-assisted nonlinear regression analysis (Accufit and Accucomp, Lunden Software, Chagrin Falls, OH). $IC_{50}$ values were converted to $K_i$ values using the Cheng-Prusoff equation (*Biochem. Pharmacol.*, **22**, 3099-3108 (1973). All experiments were performed in triplicate. The results of these binding experiments are summarized in Table I. The values represent $K_i$ in nM, numbers in parentheses represent % displacement at 30 nM.

TABLE I

| Compound of Example | $K_i$ | Compound of Example | $K_i$ | Compound of Example | $K_i$ |
|---|---|---|---|---|---|
| 1 | (78%) | 19 | (26%) | 37 | (66%) |

| | | | | | |
|---|---|---|---|---|---|
| 2 | 2.8 | 20 | ______ | 38 | (42%) |
| 3 | (74%) | 21 | (26%) | 39 | (19%) |
| 4 | (74%) | 22 | (38%) | 40 | 10.5 |
| 5 | 82.0 | 23 | (33%) | 41 | (27%) |
| 6 | 56.0 | 24 | ______ | 42 | (62%) |
| 7 | (13%) | 25 | (30%) | 43 | (67%) |
| 8 | 49.5 | 26 | (26%) | 44 | 6.8 |
| 9 | 347.0 | 27 | (31%) | 45 | 8.0 |
| 10 | 6.1 | 28 | (31%) | 46 | 209.0 |
| 11 | (68%) | 29 | (52%) | 47 | 3.3 |
| 12 | 6.3 | 30 | (48%) | 48 | ______ |
| 13 | (70%) | 31 | (23%) | 49 | 13.0 |
| 14 | (54%) | 32 | ______ | 50 | 23.5 |
| 15 | (30%) | 33 | 119 | 51 | 212.0 |
| 16 | (21%) | 34 | 364 | 52 | 2.1 |
| 17 | (51%) | 35 | 202 | 53 | 23.0 |
| 18 | (44%) | 36 | 33 | | |

As was reported by R.L. Weinshank, *et al.*, WO93/14201, the $5\text{-HT}_{1F}$ receptor is functionally coupled to a G-protein as measured by the ability of serotonin and serotonergic drugs to inhibit forskolin stimulated cAMP production in NIH3T3 cells transfected with the $5\text{-HT}_{1F}$ receptor. Adenylate cyclase activity was determined using standard techniques. A maximal effect is achieved by serotonin. An $E_{max}$ is determined by dividing the inhibition of a test compound by the maximal effect and determining a percent inhibition. (N. Adham, *et al.*, *supra*,; R.L. Weinshank, *et al.*, *Proceedings of the National Academy of Sciences (USA)*, **89**,3630-3634 (1992)), and the references cited therein.

Measurement of cAMP formation

Transfected NIH3T3 cells (estimated Bmax from one point competition studies=488 fmol/mg of protein) were incubated in DMEM, 5 mM theophylline, 10 mM HEPES (4-[2-hydroxyethyl]-1-piperazineethanesulfonic acid) and 10 µM pargyline for 20 minutes at 37°C, 5% $CO_2$. Drug dose-effect curves were then

conducted by adding 6 different final concentrations of drug, followed immediately by the addition of forskolin (10 μM). Subsequently, the cells were incubated for an additional 10 minutes at 37°C, 5% $CO_2$. The medium was aspirated and the reaction was stopped by the addition of 100 mM HCl. To demonstrate competitive antagonism, a dose-response curve for 5-HT was measured in parallel, using a fixed dose of methiothepin (0.32 μM). The plates were stored at 4°C for 15 minutes and then centrifuged for 5 minutes at 500 x g to pellet cellular debris, and the supernatant was aliquoted and stored at -20°C before assessment of cAMP formation by radioimmunoassay (cAMP radioimmunoassay kit; Advanced Magnetics, Cambridge, MA). Radioactivity was quantified using a Packard COBRA Auto Gamma counter, equipped with data reduction software. All of the compounds exemplified were tested and found to be agonists at the 5-$HT_{1F}$ receptor in the cAMP assay.

Selectivity data for different four serotonin receptors is shown below in Table 2:

| Compound of Example | $5HT_{1a}$ | $5HT_{1d\alpha}$ | $5HT_{1d\beta}$ | $5HT_{1F}$ |
|---|---|---|---|---|
| 2 | 6.1nM | 38.3nM | 182.8nM | 2.8nM |
| 10 | -- | 298.9 | 158.8 | 6.1 |
| 12 | -- | 138.5 | 51.7 | 6.3 |
| 40 | -- | 15.3 | 19.6 | 10.5 |
| 45 | 9.4 | -- | -- | 8.0 |
| 47 | 9.4 | 87.2 | 409.1 | 3.3 |
| 48 | 10.8 | 68 | 278.8 | 1.3 |
| 51 | 12.5 | -- | -- | 211.5 |
| 52 | 1.7 | 50.4 | 225.7 | 2.1 |

The discovery that the pain associated with migraine and associated disorders is inhibited by agonists of the 5-$HT_{1F}$ receptor required the analysis of data from diverse assays of

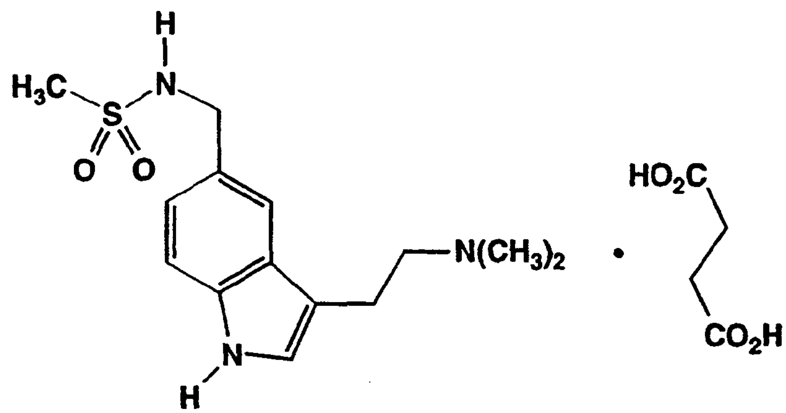
pharmacological activity. To establish that the 5-$HT_{1F}$ receptor subtype is responsible for mediating neurogenic meningeal extravasation which leads to the pain of migraine, the binding affinity of a panel of compounds to serotonin receptors was measured first, using standard procedures. For example, the ability of a compound to bind to the 5-$HT_{1F}$ receptor subtype was performed as described *supra*. For comparison purposes, the binding affinities of compounds to the 5-$HT_{1D\alpha}$, 5-$HT_{1D\beta}$, 5-$HT_{1E}$ and 5-$HT_{1F}$ receptors were also determined as described *supra*, except that different cloned receptors were employed in place of the 5-$HT_{1F}$ receptor clone employed therein. The same panel was then tested in the cAMP assay to determine their agonist or antagonist character. Finally, the ability of these compounds to inhibit neuronal protein extravasation, a functional assay for migraine pain, was measured.

The panel of compounds used in this study represents distinct structural classes of compounds which were shown to exhibit a wide range of affinities for the serotonin receptors assayed. Additionally, the panel compounds were shown to have a wide efficacy range in the neuronal protein extravasation assay as well. The panel of compounds selected for this study are described below.

Compound I

3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulfonamide butane-1,4-dioate (1:1)

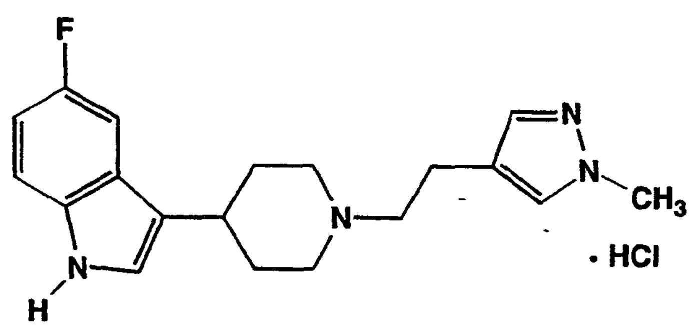
(Sumatriptan succinate)



Sumatriptan succinate is commercially available as Imitrex™ or may be prepared as described in United States Patent 5,037,845, issued August 6, 1991, which is herein incorporated by reference.

Compound II

5-fluoro-3-<1-<2-<1-methyl-1H-pyrazol-4-yl>ethyl>-4-piperidinyl>-1H-indole hydrochloride



Compound II is available by the following procedure.

2-(1-methyl-3-pyrazolo)-1-ethanol

To a mixture of 200 gm (2.85 mole) 2,3-dihydrofuran and 800 mL (4.81 mole) triethylorthoformate were added 0.8 mL (6.5 mMol) boron trifluoride diethyl etherate dropwise. After an initial exotherm the reaction mixture was allowed to stir at ambient temperature for four days. To the reaction mixture was then added 4.0 gm potassium carbonate and the reaction mixture was distilled under 6.0 mm Hg. Fractions

distilling between 60°C and 130°C were collected to give 261.64 gm (42.1%) of a light yellow oil.
MS(m/e): 219($M^+$)

To a solution of 87.2 gm (0.40 mole) of the previously prepared yellow oil in 787 mL 1N HCl were added 21.3 mL (0.40 mole) methyl hydrazine and the reaction mixture was stirred at reflux for four hours. The reaction mixture was cooled to ambient temperature and the volatiles were removed under reduced pressure. The residual oil was treated with 2N NaOH until basic and the aqueous extracted well with dichloromethane. The combined organic extracts were dried over sodium sulfate and concentrated under reduced pressure to give 32.15 gm (64.5%) of the title compound as a brown oil.
MS(m/e): 126($M^+$)
$^1$H-NMR(DMSO-$d_6$): δ7.45 (s, 1H); 7.25 (s, 1H); 4.65 (t, 1H); 3.75 (s,3H); 3.55 (m, 2H); 2.55 (t, 2H).

1-methyl-4-(2-methanesulfonyloxyethyl)pyrazole

To a solution of 16.0 gm (127 mMol) 2-(1-methyl-3-pyrazolo)-1-ethanol and 27 mL (193 mMol) triethylamine in 550 mL tetrahydrofuran were added 10.8 mL (140 mMol) methanesulfonyl chloride with icebath cooling. Once the addition was complete, the reaction mixture was stirred at ambient for 4 hours. The volatiles were then removed under reduced pressure and the residue partitioned between water and dichloromethane. The organic phase was washed with water followed by saturated aqueous sodium chloride and the remaining organics dried over sodium sulfate. The solvent was removed under reduced pressure to give a crude yield of 28.4 gm of the title compound as a brown oil. The product was used without further purification.

5-fluoro-3-[1,2,3,6-tetrahydro-4-pyridyl]-1H-indole

To a solution of 74 gm potassium hydroxide in 673 mL methanol were added 10.0 gm (74 mMol) 5-fluoroindole and 23.3 gm (151 mMol) 4-piperidone•HCl•$H_2O$. The reaction mixture was

stirred at reflux for 18 hours. The reaction mixture was diluted with 1.3 L of water and the resulting precipitate recovered by filtration and dried under reduced pressure to give 10.75 gm (67.2%) of 5-fluoro-3-[1,2,5,6-tetrahydro-4-pyridyl]-1H-indole as a yellow solid.

5-fluoro-3-(4-piperidinyl)-1H-indole

To a solution of 10.75 gm (50 mMol) 5-fluoro-3-[1,2,5,6-tetrahydro-4-pyridyl]-1H-indole in 500 mL ethanol were added 2.0 gm 5% palladium on carbon and the reaction mixture hydrogenated at ambient temperature for 18 hours at an initial hydrogen pressure of 60 p.s.i. The reaction mixture was then filtered through a pad of celite and the filtrate concentrated under reduced pressure to give an off-white solid. The solid was recrystallized from methanol to give 8.31 gm (76.2%) of the title compound as a colorless solid.

m.p.=229-230°C.

MS(m/e): 218($M^+$)

Calculated for $C_{13}H_{15}N_2F$: Theory: C, 71.53; H, 6.93; N, 12.83. Found: C, 71.81; H, 7.02; N, 12.80.

Alkylation

To a solution of 2.0 gm (9.2 mMol) 5-fluoro-3-(4-piperidinyl)-1H-indole and 2.4 gm (23 mMol) sodium carbonate in 50 mL dimethylformamide were added 1.87 gm (9.2 mMol) 1-methyl-4-(2-methanesulfonyloxyethyl)pyrazole in 5 mL dimethylformamide. The reaction mixture was stirred at 100°C for 18 hours. The reaction mixture was cooled to ambient and the solvent removed under reduced pressure. The residue was partitioned between dichloromethane and water and the phases separated. The organic phase was washed well with water followed by saturated aqueous sodium chloride. The remaining organic phase was dried over sodium sulfate and concentrated under reduced pressure. The residual oil was subjected to silica gel chromatography, eluting with 20:1 dichloromethane:methanol. Fractions shown to contain the desired compound were combined and concentrated under reduced pressure to give a yellow oil. The oil was converted to the hydrochloride salt and was crystallized from ethyl acetate/methanol. 1.61 gm (51.1%) of Compound II were recovered as colorless crystals.

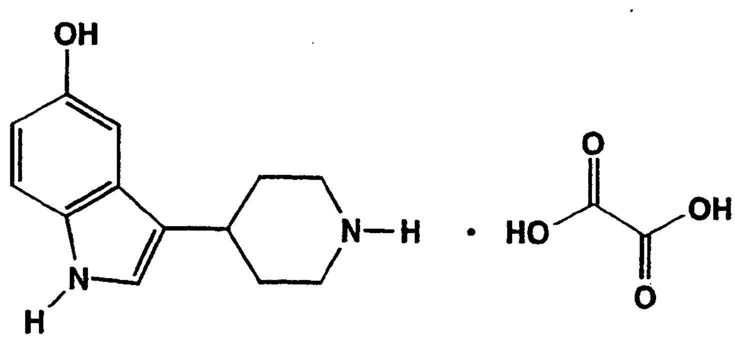
m.p.=239°C.

MS(m/e): 326($M^+$)

Calculated for $C_{19}H_{23}N_4F{\cdot}HCl$: Theory: C, 62.89; H, 6.67; N, 15.44. Found: C, 62.80; H, 6.85; N, 15.40.

Compound III

5-hydroxy-3-(4-piperidinyl)-1H-indole oxalate



Compound III is available by the following procedure.

5-benzyloxy-3-[1,2,5,6-tetrahydro-4-pyridinyl]-1H-indole

Starting with 5.0 gm (22 mMol) 5-benzyloxyindole and 6.88 gm (45 mMol) 4-piperidone•HCl•$H_2O$, 6.53 gm (97.6%) of 5-benzyloxy-3-[1,2,5,6-tetrahydro-4-pyridinyl]-1H-indole were recovered as a light yellow solid by the procedure described in Preparation I. The material was used in the subsequent step without further purification.

Hydrogenation/Hydrogenolysis

To a solution of 1.23 gm (4 mMol) 5-benzyloxy-3-[1,2,5,6-tetrahydro-4-pyridinyl]-1H-indole in 50 mL 1:1 tetrahydrofuran:ethanol were added 0.3 gm 5% palladium on carbon and the reaction mixture hydrogenated at ambient temperature for 18 hours with an initial hydrogen pressure of 60 p.s.i. The reaction mixture was then filtered through a celite pad and the filtrate concentrated under reduced pressure. The residue was converted to the oxalate salt and 0.98 gm (80.0%) of Compound III were recovered as a brown foam.

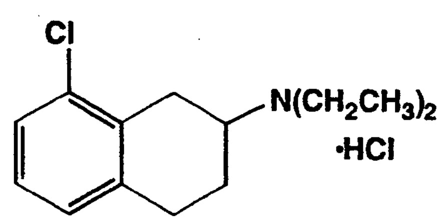
m.p.=67°C

MS(m/e): 216($M^+$)

Calculated for $C_{13}H_{16}N_2O{\bullet}C_2H_2O_4$: Theory: C, 58.81; H, 5.92; N, 9.14. Found: C, 58.70; H, 5.95; N, 9.39.

Compound IV

8-chloro-2-diethylamino-1,2,3,4-tetrahydronaphthalene hydrochloride




Compound IV is available by the following procedure.

8-chloro-2-tetralone

A mixture of 30.0 gm (0.176 mole) of o-chlorophenyl-acetic acid and 40.0 mL of thionyl chloride was stirred at

ambient temperature for 18 hours. The volatiles were then removed in vacuo to give 32.76 gm (99.0 %) of o-chlorophenylacetyl chloride as a transparent, pale yellow, mobile liquid.

NMR($CDCl_3$): 7.5-7.1 (m, 4H), 4.2 (s, 2H).

To a slurry of 46.5 gm (0.348 mole) $AlCl_3$ in 400 mL dichloromethane at -78°C was added a solution of 32.76 gm (0.174 mole) of the previously prepared o-chlorophenylacetyl chloride in 100 mL dichloromethane dropwise over 1 hour. The dry ice/acetone bath then was replaced with an ice/water bath and ethylene was bubbled into the reaction mixture during which time the temperature rose to 15°C. The ethylene addition was discontinued at the end of the exotherm and the reaction mixture was stirred at about 5°C for 4 hours. Ice was then added to the reaction mixture to destroy aluminum complexes. Upon termination of the exotherm, the reaction mixture was diluted with 500 mL of water and stirred vigorously until all solids had dissolved. The phases were separated and the organic phase was washed with 3x400 mL 1N hydrochloric acid and 2x400 mL saturated aqueous sodium bicarbonate. The remaining organic phase was then dried over sodium sulfate and concentrated in vacuo to give a pale orange residue. The residue was dissolved in 1:1 hexane:diethyl ether and was poured over a flash silica column which was then eluted with 1:1 hexane:diethyl ether to give a light yellow residue which was crystallized from 4:1 hexane:diethyl ether to give 10.55 gm of the title compound.

NMR($CDCl_3$): 7.5-7.2 (m, 3H), 3.7 (s, 2H), 3.3-3.0 (t, J=7 Hz, 2H), 2.8-2.4 (t, J=7 Hz, 2H).

MS: 180(60), 165(9), 138(100), 117(52), 115(50), 103(48), 89(20), 76(25), 74(18), 63(30), 57(9), 52(28), 51(20), 42(6), 39(32).

IR(nujol mull): 2950 $cm^{-1}$, 2927 $cm^{-1}$, 1708 $cm^{-1}$, 1464 $cm^{-1}$, 1450 $cm^{-1}$, 1169 $cm^{-1}$, 1141 $cm^{-1}$.

Reductive Amination

To a solution of 0.5 gm (2.78 mMol) 8-chloro-2-tetralone in 25 mL cyclohexane were added 1.4 mL (13.9 mMol) diethylamine followed by 0.1 gm p-toluenesulfonic acid monohydrate. The reaction mixture was then heated at reflux with constant water removal (Dean-Stark Trap) for 18 hours. The reaction mixture was then cooled to ambient and the volatiles removed under reduced pressure. The residue was then dissolved in 15 mL methanol to which were then added 1.5 mL acetic acid followed by the portionwise addition of 0.5 gm sodium borohydride. The reaction mixture was then stirred for 1 hour at ambient.

The reaction mixture was then diluted with 20 mL 10% HCl and stirred for an additional hour. The mixture was then extracted with diethyl ether and the remaining aqueous phase was poured over ice, made basic with ammonium hydroxide and extracted well with dichloromethane. These extracts were combined, dried over sodium sulfate and concentrated under reduced pressure. The residue was redissolved in dichloromethane and subjected to chromatography over basic alumina, eluting with dichloromethane. Fractions shown to contain product were combined and concentrated under reduced pressure. The residual oil was dissolved in diethyl ether and the solution saturated with hydrogen chloride. The viscous residue was crystallized from acetone/diethyl ether to give 0.20 gm (23.2 %) of Compound IV as colorless crystals.

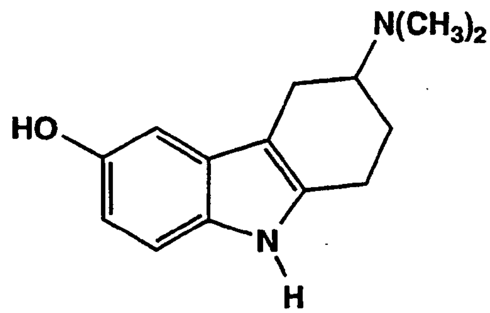
m.p.=158-159°C

MS(m/e): 273

Calculated for $C_{14}H_{21}NCl \cdot HCl$: Theory: C, 61.32; H, 7.72; N, 5.11. Found: C, 61.62; H, 7.94; N, 5.03.

Compound V

6-hydroxy-3-dimethylamino-1,2,3,4-tetrahydrocarbazole




Compound V is available by the following procedure.

4-dimethylamino-1-cyclohexanone ethylene ketal

To a solution of 5.0 gm (32 mMol) 1,4-cyclohexanedione *mono*-ethylene ketal and 10.80 gm (240 mMol) dimethylamine were added 2.0 mL acetic acid and the mixture was stirred at $0^{o}C$ for 1.5 hours. To this solution were then added 3.62 gm (58 mMol) sodium cyanoborohydride and the reaction stirred for an additional hour at ambient. The pH of the reaction mixture was adjusted to ~7 with 16 mL acetic acid and stirred 18 hours at ambient. The volatiles were removed under reduced pressure and the residue dissolved in cold 5% tartaric acid solution and then the aqueous phase was made basic with 5N sodium hydroxide. This aqueous phase was extracted well with dichloromethane. These organic extracts were combined and concentrated under reduced pressure to give 5.04 gm (85%) of the title compound as an oil.

4-dimethylamino-1-cyclohexanone

4.96 gm (26.8 mMol) 4-dimethylamino-1-cyclohexanone ethylene ketal were dissolved in 50 mL formic acid and the solution stirred at reflux for 18 hours. The reaction mixture was then cooled to ambient and the volatiles removed under reduced pressure to give 3.78 gm (100%) of the title compound.

6-benzyloxy-3-dimethylamino-1,2,3,4-tetrahydrocarbazole

To a solution of 3.78 gm (26.8 mMol) 4-dimethylamino-1-cyclohexanone and 6.69 gm (26.8 mMol) 4-benzyloxyphenyl-

hydrazine hydrochloride in 50 mL ethanol were added 2.17 mL (26.8 mMol) pyridine. To this solution were added 5x10 mL portions of water and the reaction mixture then stored at 0$^{o}$C for 18 hours. The reaction mixture was then diluted with an additional 50 mL of water and the mixture extracted well with dichloromethane. The combined organic extracts were dried over sodium sulfate and the volatiles removed under reduced pressure. The residual oil was subjected to flash silica gel chromatography, eluting with 9:1 chloroform:methanol. Fractions shown to contain the desired product were combined and concentrated under reduced pressure to give 2.14 gm (24.9%) of the title compound.

Hydrogenolysis

To a solution of 2.14 gm (6.7 mMol) 6-benzyloxy-3-dimethylamino-1,2,3,4-tetrahydrocarbazole in 50 mL ethanol were added 0.20 gm 10% palladium on carbon and the reaction mixture was hydrogenated at ambient temperature with an initial hydrogen pressure of 40 p.s.i. After 5 hours an additional charge of 0.20 gm 10% palladium on carbon were added and the reaction mixture repressurized with hydrogen to 40 p.s.i. for 4 hours. The reaction mixture was then filtered through a pad of celite and the filtrate concentrated under reduced pressure. The residue was subjected to Florisil chromatography, eluting with 9:1 chloroform:methanol. Fractions shown to contain the desired compound were combined and concentrated under reduced pressure. The residue was again subjected to Florisil chromatography, eluting with a gradient consisting of chloroform containing 2-10% methanol. Fractions shown to contain product were combined and concetnrated under reduced pressure to give Compound V as a crystalline solid.

MS(m/e): 230($M^+$)

Calculated for $C_{14}H_{18}N_2O$: Theory: C, 73.01; H, 7.88; N, 12.16. Found: C, 72.75; H, 7.83; N, 11.97.

Binding Assays

The binding affinities of compounds for various serotonin receptors were determined essentially as described

above except that different cloned receptors are employed in place of the $5\text{-HT}_{1F}$ receptor clone employed therein. The results of these binding experiments are summarized in Table III.

TABLE III

BINDING TO SEROTONIN ($5\text{-HT}_1$) RECEPTOR SUBTYPES ($K_i$ nM)

| Compound | $5\text{-HT}_{1D\alpha}$ | $5\text{-HT}_{1D\beta}$ | $5\text{-HT}_{1E}$ | $5\text{-HT}_{1F}$ |
|---|---|---|---|---|
| I | 4.8 | 9.6 | 2520.0 | 25.7 |
| II | 21.7 | 53.6 | 50.3 | 2.5 |
| III | 163.2 | 196.5 | 3.9 | 22.0 |
| IV | 13.5 | 145.3 | 813.0 | 129.2 |
| V | 791.0 | 1683.0 | 73.6 | 10.3 |

cAMP Formation

All of the compounds of the panel were tested in the cAMP formation assay described *supra* and all were found to be agonists of the $5\text{-HT}_{1F}$ receptor.

Protein Extravasation

Harlan Sprague-Dawley rats (225-325 g) or guinea pigs from Charles River Laboratories (225-325 g) were anesthetized with sodium pentobarbital intraperitoneally (65 mg/kg or 45 mg/kg respectively) and placed in a stereotaxic frame (David Kopf Instruments) with the incisor bar set at -3.5 mm for rats or -4.0 mm for guinea pigs. Following a midline sagital scalp incision, two pairs of bilateral holes were drilled through the skull (6 mm posteriorly, 2.0 and 4.0 mm laterally in rats; 4 mm posteriorly and 3.2 and 5.2 mm laterally in guinea pigs, all coordinates referenced to bregma). Pairs of stainless steel stimulating electrodes (Rhodes Medical Systems, Inc.) were lowered through the holes in both hemispheres to a depth of 9 mm (rats) or 10.5 mm (guinea pigs) from dura.

The femoral vein was exposed and a dose of the test compound was injected intravenously (1 mL/kg). Approximately 7 minutes later, a 50 mg/kg dose of Evans Blue, a fluorescent

dye, was also injected intravenously. The Evans Blue complexed with proteins in the blood and functioned as a marker for protein extravasation. Exactly 10 minutes post-injection of the test compound, the left trigeminal ganglion was stimulated for 3 minutes at a current intensity of 1.0 mA (5 Hz, 4 msec duration) with a Model 273 potentiostat/galvanostat (EG&G Princeton Applied Research).

Fifteen minutes following stimulation, the animals were killed and exsanguinated with 20 mL of saline. The top of the skull was removed to facilitate the collection of the dural membranes. The membrane samples were removed from both hemispheres, rinsed with water, and spread flat on microscopic slides. Once dried, the tissues were coverslipped with a 70% glycerol/water solution.

A fluorescence microscope (Zeiss) equipped with a grating monochromator and a spectrophotometer was used to quantify the amount of Evans Blue dye in each sample. An excitation wavelength of approximately 535 nm was utilized and the emission intensity at 600 nm was determined. The microscope was equipped with a motorized stage and also interfaced with a personal computer. This facilitated the computer-controlled movement of the stage with fluorescence measurements at 25 points (500 μm steps) on each dural sample. The mean and standard deviation of the measurements was determined by the computer.

The extravasation induced by the electrical stimulation of the trigeminal ganglion was an ipsilateral effect (i.e. occurs only on the side of the dura in which the trigeminal ganglion was stimulated). This allows the other (unstimulated) half of the dura to be used as a control. The ratio of the amount of extravasation in the dura from the stimulated side compared to the unstimulated side dura was calculated. Saline controls yielded a ratio of approximately 2.0 in rats and 1.8 in guinea pigs. In contrast, a compound which effectively prevented the extravasation in the dura from the stimulated side would have a ratio of approximately 1.0. A dose-response curve was generated and the dose that

inhibited the extravasation by 50% ($ID_{50}$) was approximated. This data is presented in Table IV.

Table IV

Inhibition of Protein Extravasation ($ID_{50}$ mMol/kg)

| **Compound** | **i.v. $ID_{50}$ (mMol/kg)** |
|---|---|
| I | $2.6x10^{-8}$ |
| II | $8.6x10^{-10}$ |
| III | $8.9x10^{-9}$ |
| IV | $1.2x10^{-7}$ |
| V | $8.7x10^{-9}$ |

To determine the relationship of binding at various serotonin receptors to inhibition of neuronal protein extravasation, the binding affinity of all of the compounds to each of the $5\text{-}HT_{1D\alpha}$, $5\text{-}HT_{1D\beta}$, $5\text{-}HT_{1E}$ and $5\text{-}HT_{1F}$ receptors was plotted against their $ID_{50}$ in the protein extravasation model. A linear regression analysis was performed on each set of data and a correlation factor, $R^2$, calculated. The results of this analysis are summarized in Table V.

Table V

Correlation Factor ($R^2$) for Specific 5-$HT_1$ Subtype Binding Affinity vs Inhibition of Protein Extravasation

| **5-$HT_1$ Subtype** | **Correlation Factor ($R^2$)** |
|---|---|
| 5-$HT_{1D\alpha}$ | 0.07 |
| 5-$HT_{1D\beta}$ | 0.001 |
| 5-$HT_{1E}$ | 0.31 |
| 5-$HT_{1F}$ | 0.94 |

An ideally linear relationship would generate a correlation factor of 1.0, indicating a cause and effect relationship between the two variables. The experimentally determined correlation factor between inhibition of neuronal protein extravasation and 5-$HT_{1F}$ binding affinity is 0.94. This nearly ideal dependence of the $ID_{50}$ in the protein extravasation model on binding affinity to the 5-$HT_{1F}$ receptor clearly demonstrates that the 5-$HT_{1F}$ receptor mediates the inhibition of protein extravasation resulting from stimulation of the trigeminal ganglia.

What is claimed is:

1. A process for serially making a library of pharmaceutically useful compounds of the general formula:

$$\begin{array}{c} R^2 - \underset{\displaystyle A}{\underset{|}{N}} - X - R^1 \end{array}$$

wherein A is an indole analog;

X is a bond, or X is carbonyl, or thiocarbonyl;

$R^1$ is hydrogen, $C_1$-$C_6$ alkyl, aryl, cycloalkyl, heterocycle $NR^3R^4$ or $OR^5$;

$R^2$ is hydrogen, $C_1$-$C_6$ alkyl, aryl, cycloalkyl, heterocycle or a substituted analog of any of the above; with the provision that $R^1$ and $R^2$ are not both hydrogen when X is a bond;

R3 and R4 are each individually hydrogen, C1-C6 alkyl, aryl cycloalkyl, heterocycle or a substituted analog of any of the above; and

$R^5$ is hydrogen, $C_1$-$C_6$ alkyl, aryl, cycloalkyl or a substituted analog of any of the above;

said process comprising the steps of:

a) providing a first reagent in solution phase of the general formula:

$$A\text{-}NHR^2;$$

b) providing a series of second solution phase reagents each one of the general formulas:

(i) $Y\text{-}X\text{-}R^1$ wherein Y is a halogen and X i not a bond; or

(ii) $Z\text{-}N\text{-}R^1$ wherein Z is =C=O, =C=S or $R^1$-C(O)Y; and

c) sequentially mixing a predetermined quantity of said first reagent with predetermined quantities of diverse molecules of said second reagents to create a library of Formula (I) compounds.

2. The process of Claim 1 wherein step (c) includes adding an excess of each said second reagents, then adding a scavenging agent, wherein excess unreacted second reagents are consumed and tethered to a solid phase.

3. The process of Claim 2 and an additional step (d) of filtering off the solid phase.

4. The process of Claim 1 wherein step (c) is conducted in a multiple well reaction vessel, and a single one of the second reagents is introduced into each of the multiple wells.

5. The process of Claim 1 wherein each second reagent is of the general formula:

   $Y-X-R^1$ wherein X is carbonyl, and $R^1$ is $NR^3R^4$.

6. The process of Claim 1 wherein each second reagent is of the general formula:

   $Y-X-R^1$ where X is carbonyl and $R^1$ is $OR^5$.

7. The process of Claim 1 wherein each second reagent is of the formula:

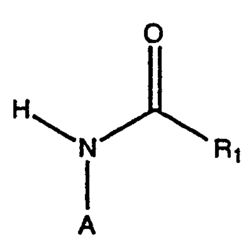
   $Y-X-R^1$ where $R^1$ is hydrogen, $C_1-C_6$ alkyl, aryl, cycloalkyl, heterocycle, or substituted analog thereof.

8. The process of Claim 1 wherein each second reagent is of the general formula:

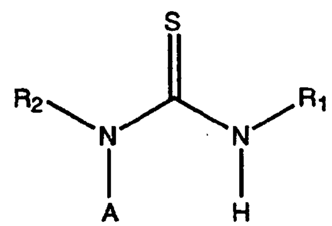
   $Z-N-R^1$ where Z is carbonyl.

9. The process of Claim 1 wherein $R^2$ is hydrogen.

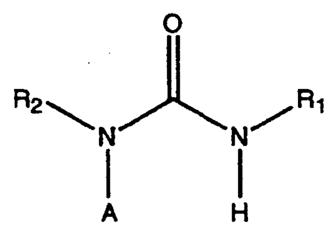
10. The process of Claim 9 wherein the formula (I) compounds have the structure:



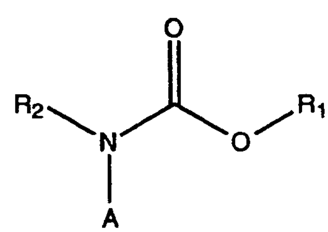
11. The process of Claim 9 wherein the formula (I) compounds have the structure:



12. The process of Claim 9 wherein the formula (I) compounds have the following structure:



13. The process of Claim 9 wherein the formula (I) compounds have the following structure:



14. A process for preparing a library of structurally diverse compounds, said process comprising the steps of:

a) providing a first reagent in solution phase;

b) providing a second reagent in solution phase, with the first and second reagents capable of reacting to form a product;

c) mixing said first reagent with an adequate amount of the second reagent to facilitate a complete reaction and form a mixture;

d) adding a solid phase-supported scavenger reagent to the mixture to remove unreacted quantities of said second reagent wherein the scavenger reagent reacts with the second reagent to form a solid support tethered compound; and

e) separating the product from the solid support tethered compound.

15. The process of Claim 14 wherein step d) includes adding a polymeric resin bound scavenger reagent to the mixture, and step e) includes separating the solid support tethered compound from the product by filtration.

16. The process of Claim 15 wherein steps a) and b) include providing a plurality of structurally diverse first and second reagents wherein a plurality of structurally diverse products are formed.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/10454

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 209/40, 401/00
US CL :546/201; 548/483
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/201; 548/483

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 5,300,506 A (SMITH ET AL) 05 April 1994, see entire document, especially Example 2 at column 14, line 20. | 1, 6, 9, 10, 13 |
| X<br>--<br>Y | US 5,145,845 (JOHNSON ET AL) 08 September 1992, see column 20, lines 43-68. | 1, 8, 9, 11, 12<br>-------------<br>1-13 |
| Y | US 4,839,377 A (BAYS ET AL) 13 June 1989, see entire document, especially column 4 beginning at line 42. | 1-13 |
| Y | US 4,552,954 A (MOESCHLER ET AL) 12 November 1985, see entire document, especially column 4, lines 3-31. | 2, 3, 14-16 |

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

12 AUGUST 1996

Date of mailing of the international search report

17 SEP 1996

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## INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/10454

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | US 4,665,037 A (STOLOWITZ) 12 May 1987, see entire document, especially Example 11 at columns 33-34. | 2, 3, 14-16 |

INTERNATIONAL SEARCH REPORT

International application No. PCT/US96/10454

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/10454

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-13, drawn to a process for seriously making a library of compounds.
Group II, claim(s) 14-16, drawn to a process for preparing a library of compounds.

The inventions listed as Groups I and II do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: In the invention of group I, there exists a special technical feature of an indole bonded to a nitrogen atom that is present in each of the process claims. However, in the invention of group II, no such special technical feature exists. Moreover, this invention can apply to a process for preparing a library of any compounds, not limited to indoles bonded to a nitrogen atom as in the invention of Group I.